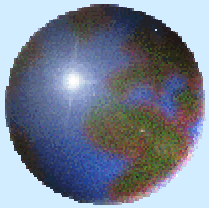


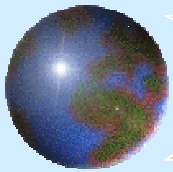
Regulatory Harmonization in a Global Environment

Alan E. Williams, Ph.D.
Director, Division of Blood Applications
Center for Biologics Evaluation Research
US Food and Drug Administration

Vision for CBER, FDA

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

- Protect and improve public and individual health in the US and, where feasible, globally
- Facilitate the development, approval and access to safe and effective products and promising new technologies
- Strengthen CBER as a preeminent regulatory organization for biologics



Vision for CBER, FDA

CBER supports international harmonization efforts ……..

- ***We live in a global environment with continuing health challenges***
- ***Harmonization generally favors improved product quality, safety, and availability***
  - ***Uniform standards***
  - ***Economic efficiency***
  - ***Global marketing***

Outline

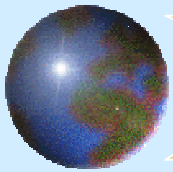
- What factors favor regulatory harmonization?
- What factors complicate regulatory harmonization? (One size may may not fit all!)
- Non-economic drivers
- Where are we now?
- Possible paths forward
- Conclusion

What factors favor regulatory harmonization?

- Sound Science

Relationship of scientific knowledge to international harmony may be bimodal…

- Validated science promotes harmony (NAT testing, heat inactivation of derivatives)
- Uncertainty regarding the application of science may lead to disharmony (ULR, plasma freezing/storage)
- Insufficient science → use of precautionary principle - may promote fragile harmony (vCJD-related geographic deferrals)



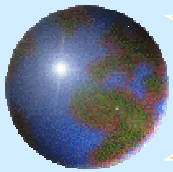
What factors favor regulatory harmonization?

- Sound Science (cont.)
  - Good standards developed anywhere may advance product quality, patient safety and public health everywhere
  - Scientific advancements often arise from international collaborations
  - A global desire to improve blood safety and availability favors harmonization of standards

What factors favor regulatory harmonization?

- A “national” donor base is relative since donors may have recently traveled from anywhere (“Global Village” concept)

- In the future, it may be critical to derive therapeutic plasma from the an EID-focus anywhere in the world. (SARS, avian flu)

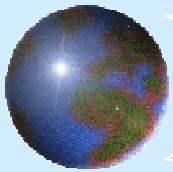


What factors favor regulatory harmonization?

- National blood systems that are internally harmonized foster international extension.
  - Intra-Nationally – donor screening and laboratory testing generally not targeted.
  - Internationally – donor screening and laboratory testing may be highly targeted

What factors favor regulatory harmonization?

- Less-developed countries may have the opportunity to "technology-hop" at greatly reduced cost. (e.g. cell phones and fingerprint donor identification systems in China, ((future blood pathogen-reduction technologies))



Complications in Reaching Regulatory Harmonization - Legal/Economic

- National interests may not coincide
  - Goals of self-sufficiency
  - Desire to nurture national industries
  - Different pathways to product approval have merit
  - Regulatory bodies are held accountable for their decisions. If global harmonization becomes a major foundation of national regulatory policy, this relationship may not be viewed favorably in the event of a subsequent national health crisis.

Complications in Reaching Regulatory Harmonization - Legal/Economic (cont.)

- National laws and pre-existing policies
  - (e.g FD&C Act, PHS Act, Regulations, Guidances)
- There is likely to be an inherent time lag and uncertainty of outcome when undertaking the modification of existing national laws
- Manufacturing differences may be deeply-rooted (e.g. single vs. dual plasma stream for derivatives;, hard vs. soft spin platelet preparation)

Complications in Reaching Regulatory Harmonization - Scientific

- Epidemiological differences matter
  - e.g. malaria, Chagas' Disease, vCJD, West Nile, future unpredictable EIDs)
- Quality of data. It is generally unacceptable to import transfusion risks (known or unknown) that exceed those inherent in a local/national donorbase

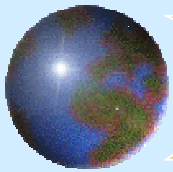
Complications in Reaching Regulatory Harmonization - Social/Societal

- Diverse social and economic conditions can affect blood policy
  - Safety and acceptability of paid donors
  - Cost:benefit for leukocyte reduction and NAT
  - Predictive value of donor questions
  - Acceptance of risk

Non-economic drivers toward harmonization

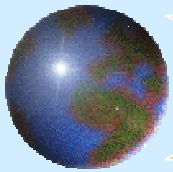
- Political leaders increasingly are accountable for blood safety decisions
  - The AIDS crisis had political repercussions in many countries including France, Canada and the U.S.
  - Similar debates are ongoing for Hepatitis C
- National regulators are increasingly aware of each others' scientific assessments and policy choices
- Harmonization may reduce political vulnerability…

  … but must be accomplished without compromising national health.



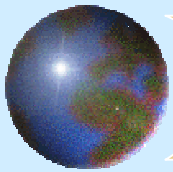
Non-economic drivers toward harmonization

- Well-considered international standards may advance national product quality and public health and are usually defensible in the national context. They may also be tied to larger harmonization efforts , e.g. EU.
- External accreditation can increase national prestige and enhance support for blood systems
- Scientific advancements often arise from international collaborations



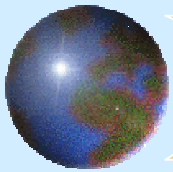
Semi-formal regulatory initiatives …..

- A number of transnational authorities have been created (e.g. European Union, TransTasmin Agency)
- Regional cooperation encourages regulatory harmonization
  - Caribbean blood standards
  - US bilateral meetings with Canada and Mexico
- WHO activities foster development of international regulatory standards



Where are we now? – US Nationally

- Achieved harmonization on a standardized, cognitively-tested FDA-accepted donor screening instrument.
  - Defined pathway for validating abbreviated instrument
- FDA formal acceptance of voluntary industry standards
  - Labeling (Codabar and ISBT 128)
  - Circular of Information
- FDA liaison with numerous voluntary industry standards
  - Vaccines and medications
  - History of cancer
  - Bacterial culture



Where are we now? – US Nationally

- Near-harmonization on vCJD geographic deferrals
- Less harmony regarding universal leukoreduction, quality assurance monitoring.
- “Opportunities” for harmonization on plasma collection, processing and storage.

Where are we now? - Internationally

- Outside of the EU, no current mechanism exists by which the major global regulatory authorities co-develop their requirements. However…
  - Governmental bodies are free to comment on each others' public documents
  - Government representatives meet in a variety of venues to exchange ideas and to collaborate on common initiatives
  - Blood standards developed by WHO, the Council of Europe, AABB and other non-governmental bodies are used internationally

The ICH Process

- The International Committee on Harmonization (ICH) was successful in standardizing many elements of drug and biologics applications, however:
  - The ICH process was very expensive and was extensively supported by the pharmaceutical industry
    - Focuses on technical aspects of product registration, especially for biotech products
  - ICH does not include the blood industry
  - ICH activities addressed blood only secondarily (e.g. Common Technical Document)

FDA's Global Engagements: Overview

- FDA engages in numerous and diverse harmonization-related activities
  - Mutual recognition agreements for inspections
  - Global Harmonization Task Force on devices
    - Classification of IVD's
  - Bilateral agreements for information sharing
  - Multilateral discussions of regulatory issues
  - WHO meetings (e.g. Expert Committee for Biological Standards, Global Collaboration for Blood Safety)
  - Other multinational initiatives (PPTA EID Roundtable; EPFA/PEI/SoGAT meeting; ISTH)

FDA's Global Engagements: MOU's

- FDA has negotiated Memoranda of Understanding (MOU's) on information sharing with several outside regulatory agencies (EMEA, Health Canada, SwissMedic)
  - Each MOU is a unique bilateral agreement
  - The agreements will permit sharing of confidential product information including applications, however, trade secret information cannot be shared without prior permission from the regulated industry
  - The framework agreements remain to be developed into operational procedures, and the scope of information sharing is under discussion

FDA's Global Engagements: WHO

- Cooperation with World Health Organization
  - FDA is a WHO Collaborating Center for Biological Standardization
    - FDA provides support to the WHO Expert Committee on Biological Standardization
  - Through WHO collaboration, FDA co-develops internationally used assays, reference materials and potency standards for coagulation products, blood group substances and pathogen detection systems for blood screening
    - Similar efforts apply to vaccine standardization

FDA's Global Engagements: WHO

- In 2000, WHO established a Global Collaboration for Blood Safety (GCBS) in which FDA participates
  - The GCBS mission is to promote and strengthen international collaboration on safety of blood products and transfusion practices
  - GCBS working groups have
    - Developed fact sheets on plasma
    - Begun a pilot study of a tool to assess blood need
    - Drafted a "minimum requirements" document for use by blood transfusion services
    - Drafted an Aide-Memoire on Good Policy Practice
    - Planned a Policy Makers Forum

FDA's Global Engagements: COE

- Council of Europe (COE), European Directorate for the Quality of Medicines (EDQM)/European Pharmacopoeia (EP) sets potency and assay standards for products licensed in the EU
  - FDA has collaborated in developing joint working standards with EDQM Examples: FVIII, FIX, anti-D potency standard.
  - FDA perspective is provided on issues at regular meetings of the EDQM/EP 6B Expert Committee

FDA's Global Engagements: COE

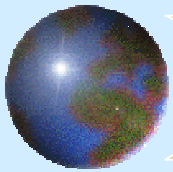
- FDA participates in the Council of Europe (COE) Select Committee of Experts on Automation and Quality Assurance in Blood Transfusion Services annual revision of the "Guide to the Preparation, Use and Quality Assurance of Blood Components."
  - The Guide is adopted in many European and some non-European states as the official standard for manufacture and use of blood components.
- FDA participation ensures US awareness of current thinking among European leaders

Possible Paths Forward

- Current initiatives show promise for improvements in communication among regulatory agencies
  - Information sharing agreements
  - More active role of WHO and industry in bringing regulators together, especially regarding EID's (e.g. vCJD, SARS, West Nile Virus)
- Expanded scientific collaborations

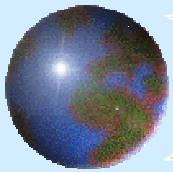
Possible Paths Forward……..

- An international dialogue on principles of (GPM) Good Policy Making
  - Transparency
  - Use of structured procedures and decision making tools
  - International communication of the scientific, economic and social basis for blood safety decisions



Possible Paths Forward……..

- Early focus on emerging policy areas before they are established in law
- Standardized nomenclature, esp epidemiology



Possible Paths Forward……..

- Define 1-2 pilot areas that may be rational targets for harmonization. Define define key parameters:
  - Available science
  - Existing national laws
  - Vested parties
  - Likelihood of broad engagement
  - Public health contribution

Conclusions

- Powerful forces favor global harmonization
  - Global desire to enhance product quality and availability, patient safety and public health
  - Economic and political factors
- Formal regulatory mechanisms to promote regulatory harmonization for blood and plasma do not exist and are unlikely to develop in the near future
  - Informal mechanisms that foster regulatory harmonization are proliferating and are gaining influence, but they still lack accountability and well-defined goals

CBER Commitment

CBER is strongly supportive of harmonization efforts that will maximize national and global health and is eager to engage in targeted interactions:

- Define future process, esp. private sector initiatives.
- Identify and move forward on 1-2 pilot areas that are achievable and will help to illuminate a path past the more difficult challenges.
- Limited CBER budget and staff availability are substantive concerns.